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Defining Refractory Pain in Cancer for Clinicians and Researchers

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Dear Editor:

Managing pain in people with cancer remains a challenge, especially in those referred to as having refractory pain. But what is refractory or intractable pain?[1,2] Until there is a standard definition there is the risk that: a) clinically, new medications are continuously added, each with diminishing returns in reducing pain, and each with an increasing likelihood of toxicity as the only noticeable change; and b) in research, there will be differing baselines for the operational definition of refractory, making it difficult to adopt the findings into practice, or to compare clinical trials in any systematic way.

Recognition of this heterogeneity led to the recognition of poor prognostic factors in pain management.[3–5] Factors contributing to pain that proves difficult to control include the underlying etiology of the pain (often reflected in the description of the pain), incident pain, concomitant psychological distress, younger age, and pain intensity. Clinical impression also indicates that patients with a prolonged period between onset of pain and initiating adequate therapy, previous long-term analgesic use for other pain, and impaired cognition (especially because it limits use of many nonpharmacological interventions) may also have pain that is more difficult to control.

Refractory pain can be defined as pain that has persisted over time despite an adequate trial of analgesic therapies and nonpharmacological approaches including the recognition and response to suffering.[6] This must specify not only medication selection but also dose and duration of use. Such a definition need not set an arbitrary time between the onset of pain and initiation of therapies nor the subsequent time before pain is labelled "refractory."

A standard definition of refractory pain requires:

- a classification of the type of pain experienced using a tool such as the Edmonton Pain classification[3,4];
- consistent use of diagnostic criteria such as the LANSS[7]; and
- a peer reviewed and agreed combination of evidence-based medications with accepted doses and duration.

The longer a person has poorly controlled pain and the more interventions that are trialled to control the pain, the greater the likelihood that the patient will be exposed to therapies without an established level I or II evidence base. Such therapies currently include combination opioid therapy, opioid rotation, the use of many co-analgesics, and complimentary therapies. As the benefit of so many of these interventions is unproven, they should ideally only be made available therapeutically in the setting of adequately designed and powered clinical trials. If a suitable trial is not available, there should be rigorous prospective evaluation for net clinical benefit including toxicity using standardized tools and data collection systems. This would require considerable reorganization of clinical practice and is an approach that would be applicable in many conditions without adequate evidence base.

Pain uncontrolled by a rigorous trial of a combination of evidence-based therapies should be the starting point for a definition of refractory. This should not include therapies with level III or lower evidence.[8]

Clinicians in hospice and palliative care often criticize their oncological colleagues for offering off-label third-, fourth-, or fifth-line anticancer therapy with rapidly diminishing benefit and a relative shift in the therapeutic ratio towards toxicity. Oncologists often defend this action on the grounds that "there is nothing else to offer." In hospice and palliative care, we are at risk of similar behavior with the treatment of refractory pain unless there is an agreed taxonomy for the diagnosis which clinicians and researchers can operationalize uniformly.

The multidimensional nature of pain, the absence of objective measures of response, and the palpable distress of severe pain all contribute particular challenges to clinicians who are intent on relieving suffering. Working toward better consistency of terminology is important for all symptoms when terms such as "refractory" are used.

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